sanofi aventis

Because health matters

April 25, 2005

Via fax and UPS

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Division of Dockets Management (HFA-305)
Food and Drug Administration
5630 Fishers Lane, Room 1061
Rockville, MD 20852

Re: Docket No. 2003N-0528

Draft Guidance for Industry on Manufacturing Biological Drug Substances, Intermediates, or Products Using Spore-Forming Microorganisms

Dear Sir/Madam:

Sanofi-Synthelabo Inc. and Aventis Pharmaceuticals, members of the sanofi-aventis Group, appreciates the opportunity to comment on the above-referenced Draft Guidance entitled "*Manufacturing Biological Drug Substances, Intermediates, or Products Using Spore-Forming Microorganisms*".

This draft guidance provides recommendations in response to changes made to the requirements for spore-forming microorganisms to allow greater flexibility in manufacturing.

We have evaluated the content of the draft guidance and offer the following comments and/or clarifications for your consideration.

GENERAL COMMENTS:

The term "you" is used throughout the guidance document; we suggest replacing this term with "manufacturer" to be consistent with the approach from other guidances.

SPECIFIC COMMENTS:

Page 4: IV.A. Facilities and Equipment: *"If multiple products are manufactured in the same area or within the same building using spore-formers, then additional criteria will apply."*

We suggest replacing "*same area*" with "*same manufacturing area*" because the term "*same area*" is too vague. Additionally, "*manufacturing area*" is the term defined in the glossary.

Page 5: IV.A.1.a. Building Construction and Configuration: *"Please refer to FDA's guidance for industry entitled "Sterile Drug Products Produced by Aseptic Processing – Current Good Manufacturing Practice," dated September 2004 (October 4, 2004, 69 FR 59258) (http://www.fda.gov/cder/guidance/5882fnl.htm), for the agency's current thinking on aseptic processing."*

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We suggest moving this reference to the end of the document or as a footnote.

Page 6: IV.A.2.b. Material Transfer: *"When it is necessary to employ an airlock system for decontamination of material that is transferred out of a facility, the decontamination process, using a liquid or gaseous agent, must be validated to inactivate the spore-formers, including decontamination agent efficacy studies."*

For clarity, please provide a clearer definition of "decontamination" and "inactivation", e.g., in the "*Guidance for Industry on Sterile Drug Products Produced by Aseptic Processing*, clear guidance for decontamination was provided: "*Normally, a four- to six-log reduction can be justified depending on the application.*"

Page 7: V. A.1.a: Building Construction and Configuration

We suggest defining the terms "*air sink*" and "*air dome*" in the glossary.

Page 11. V.D. Sampling and Testing: *"On-going sampling and testing for spore-formers in the facility, equipment, and subsequent products manufactured is important to ensure containment and cleaning procedures are continuously effective."*

The term "*on-going*" is too vague. We recommend providing some guidance on the expectations in terms of acceptable frequency of the sampling & testing for spore-formers in the facility, equipment, etc…

Page 11. V.D.1.a. Specificity: *"Testing must be able to detect the specific spore-former and identify it in the presence of other microorganisms."*

We suggest the guidance be more specific as to the type of "other microorganisms", e.g. spore-formers or any microbe?

On behalf of Sanofi-Synthelabo Inc. and Aventis Pharmaceuticals, members of the sanofi-aventis Group, we appreciate the opportunity to comment on the *Draft Guidance for Industry on Manufacturing Biological Drug Substances, Intermediates, or Products Using Spore-Forming Microorganisms* and are much obliged for your consideration.

Sincerely,

Steve Caffé, M.D.
Vice President, Head US Regulatory Affairs